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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/056,479	01/24/2002	Benjamin A. Bowen	50273/005002	5627

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,479	BOWEN ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *6 and 11-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-10* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I in the paper filed 8/11/2003 is acknowledged. Applicant's further election of the following species without traverse is also acknowledged:

with regard to cell type, election of plant cells, specifically A. reptans cells;

with regard to phenotype, election of production of terpenes;

with regard to stimulus, election of Candida;

with regard to gene, election of terpene cyclase.

Thus, in light of the election of group I and the particular species elected, claims 1-5 and 7-10 are examined herein. The remaining claims in group I (claims 6 and 11-26) are withdrawn from prosecution because they are drawn to non-elected species. These will be rejoined, as appropriate, upon finding of an allowable generic claim.

Priority

2. Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. However, the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for claims 3, 4, 7, 8, and 9 of this application. While the provisional applicant discusses the induction of diterpenes, no basis was located in the provisional application to support claims wherein the phenotype is the production of any terpene (claim 3) or monoterpenes or sesquiterpenes (claim 4). Furthermore, the provisional application does not discuss genes that encode terpene cyclases (claims 7-9).

Specification

3. The abstract of the disclosure is objected to because it contains the use of the legal term "said." Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. **The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided.** The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details (emphasis added).

Correction is required. See MPEP § 608.01(b).

Claim Objections

4. Claim 9 is objected to because of the following informalities: The claim does not end in a period. MPEP 601.01(m) states, "Each claim begins with a capital letter and ends with a period. Periods may not be used elsewhere in the claims except for abbreviations." Appropriate correction is required.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Seehaus *et al.* (Plant Molecular Biology, 1998, Vol. 38, pages 1225-1234).

Seehaus et al. teach a method of identifying a gene associated with a desired phenotype, said method comprising the steps of:

(a) providing a plurality of cell cultures, each comprising plant cells capable of exhibiting said desired phenotype (p. 1226, "Biological material");

(b) contacting the cells of step (a) with a stimulus that (i) induces said cells to exhibit said phenotype or (ii) does not induce said cells to exhibit said phenotype (p. 1226);

(c) determining the presence of the desired phenotype in cells of step (b); and

(d) identifying a gene in said cells that has increased expression in response to stimuli that induce said phenotype but does not have increased expression in response to stimuli that do not induce said phenotype, wherein said identified gene is associated with said desired phenotype.

With regard to claim 2, the cells taught by Seehaus et al. are plant cells.

Seehaus et al. teach a method for analyzing the differential expression of genes in plant cell cultures, in particular soybean cell cultures. They provide a plurality of cell cultures, including control cultures, cultures that have been treated with salicylic acid, cultures that have been inoculated with *Pseudomonas syringae* pv. *glycinea* expressing the avrA gene, and cultures that were both inoculated and treated with SA (Fig. 1). The inoculation and treatment with both SA and P. syringae induces an observable phenotype, namely a hypersensitive response. The treatment with either of these stimuli independently does not induce the hypersensitive response. Seehaus et al. identify a number of genes that have increased expression in cells in response to stimuli that induce the hypersensitive response as compared to those treatments that do not

induce the hypersensitive response (see Figure 1, Figure 2, and p. 1227). Thus, the teachings of Seehaus et al. anticipate the instant claims.

7. Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Lopez-Myer *et al.* (The Plant Journal (1997) 11(6) 1167-1175).

Lopez-Meyer et al. teach a method of identifying a gene associated with a desired phenotype, said method comprising the steps of:

(a) providing a plurality of cell cultures, each comprising plant cells capable of exhibiting said desired phenotype (p. 1170 and 1174);

(b) contacting the cells of step (a) with a stimulus that (i) induces said cells to exhibit said phenotype or (ii) does not induce said cells to exhibit said phenotype (p. 1174, figure 7);

(c) determining the presence of the desired phenotype in cells of step (b) (figure 7); and

(d) identifying a gene in said cells that has increased expression in response to stimuli that induce said phenotype but does not have increased expression in response to stimuli that do not induce said phenotype, wherein said identified gene is associated with said desired phenotype (p. 1170).

With regard to claim 2, the cells taught by Lopez-Meyer et al. are plant cells.

Lopez-Meyer et al. teach a method for analyzing the differential expression of genes in plant cell cultures, in particular cell cultures from the Chinese tree *Campototheca acuminata.* They provide a plurality of cell cultures, including control cultures and cultures that have been treated with methyl jasomonate (MeJa) (p. 4221 and figure 7). The treatment with MeJa induces an observable phenotype, namely increased tryptophan decarboxylase (TDC) activity (Figure 7b). The stimuli present in the control culture do not induce increased TDC activity. Lopez-

Meyer et al. identify a gene that has increased expression in cells in response to stimuli that induce the increased TDC activity as compared to the treatments that does not induce the increased TDC activity, namely the tdc2 gene transcript (p. 1170, second column). Thus, the teachings of Lopez-Meyer et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 3, 4, 7, 8, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wildung *et al.* (The Journal of Biological Chemistry, Vol. 271, No. 16, pages 9201-9204, 1996) in view of both Seehaus *et al.* and Walker et al. (PNAS, Jan 18 2000, Vol. 91, No. 2, pages 583-587).

Wildung et al. teach that the terpene taxol is a well established potent chemotherapeutic agent, and that "the taxadiene synthase is an obvious target for gene isolation (p. 9201, second

column)." Wildung *et al.* further teach that taxadiene synthase is a cyclization enzyme (Abstract and p. 9201, second column), thus is a taxadiene synthase is a taxadiene cyclase (which is a diterpene cyclase). Wildung et al. teach the isolation of this gene using an arbitrary primer PCR methodology (p. 9201). Wildung et al. do not teach a method of identifying a gene associated with terpene production via a differential expression analysis method which utilized differentially treated cell cultures. However, such methods were widely known in the prior art at the time the invention was made.

For example, Seehaus et al. teach a method of identifying a gene associated with a desired phenotype, said method comprising the steps of:

(a) providing a plurality of cell cultures, each comprising plant cells capable of exhibiting said desired phenotype (p. 1226, "Biological material");

(b) contacting the cells of step (a) with a stimulus that (i) induces said cells to exhibit said phenotype or (ii) does not induce said cells to exhibit said phenotype (p. 1226);

(c) determining the presence of the desired phenotype in cells of step (b); and

(d) identifying a gene in said cells that has increased expression in response to stimuli that induce said phenotype but does not have increased expression in response to stimuli that do not induce said phenotype, wherein said identified gene is associated with said desired phenotype.

Seehaus et al. teach a method for analyzing the differential expression of genes in plant cell cultures, in particular soybean cell cultures. They provide a plurality of cell cultures, including control cultures, cultures that have been treated with salicylic acid, cultures that have been inoculated with Pseudomonas syringae pv. glycinea expressing the avrA gene, and cultures

that were both inoculated and treated with SA (Fig. 1). The inoculation and treatment with SA induces an observable phenotype, namely a hypersensitive response. The treatment with either of these stimuli independently does not induce the hypersensitive response. Seehaus et al. identify a number of genes that have increased expression in cells in response to stimuli that induce the hypersensitive response as compared to those treatments that do not induce the hypersensitive response (see Figure 1, Figure 2, and p. 1227).

Furthermore, at the time the invention was made, method for inducing the phenotypic response of the production of terpenes, in particular taxol, in cell cultures were known in the prior art. For example, Walker et al. exemplify the treatment of cell suspension cultures with methyl jasomate for the induction of Taxol production (p. 583, Col. 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the gene isolation and characterization methods taught by Seehaus et al. for the study of genes related to terpene synthesis, and in particular to isolate the gene encoding taxadiene synthase. One would have been motivated by the teachings of Wildung et al. to isolate a genes involved in taxol synthesis, in particular taxadiene synthase, which Wildung et al. teach "is an obvious target for gene isolation." One would have been motivated to utilize the methods of Seehaus et al. because Seehaus et al. successfully demonstrate utilizing this method for the isolation of genes differentially expressed in phenotypic responses, and one would have been motivated to provide alternative gene isolation methods for the isolation of the obvious target the taxadiene synthase gene, as well as for other genes associated with the production of terpenes. Seehaus et al. teach that the differential display method has a distinct advantage of the simultaneous monitoring of the expression of more than two sets of samples at

one time, and describe the method as a powerful tool for the isolation of induced genes (abstract). One of ordinary skill in the art would have been motivated to practice differential expression methods for the isolation of genes involved in terpene synthesis by the success of Walker et al. in inducing the expression of taxol, as they exemplify methods for inducing and inhibiting the production of taxol. The knowledge of such methods in the prior art would have afforded one of skill in the art with the necessary methodologies to practice the methods of Seehaus et al. for the isolation of the obvious gene target taxadiene synthase. Thus, in light of the combined teachings of Wildung et al., Seehaus et al., and Walker et al., the instant invention is *prima facie* obvious.

11. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Seehaus *et al.* in view of Tanaka *et al.* (Plant Science, 1998, vol. 137, pages 95-105).

Seehaus et al. teach a method of identifying a gene associated with a desired phenotype, said method comprising the steps of:

(a) providing a plurality of cell cultures, each comprising plant cells capable of exhibiting said desired phenotype (p. 1226, "Biological material");

(b) contacting the cells of step (a) with a stimulus that (i) induces said cells to exhibit said phenotype or (ii) does not induce said cells to exhibit said phenotype (p. 1226);

(c) determining the presence of the desired phenotype in cells of step (b); and

(d) identifying a gene in said cells that has increased expression in response to stimuli that induce said phenotype but does not have increased expression in response to stimuli that do not induce said phenotype, wherein said identified gene is associated with said desired phenotype.

Seehaus et al. teach a method for analyzing the differential expression of genes in plant cell cultures, in particular soybean cell cultures. They provide a plurality of cell cultures, including control cultures, cultures that have been treated with salicylic acid, cultures that have been inoculated with Pseudomonas syringae pv. glycinea expressing the avrA gene, and cultures that were both inoculated and treated with SA (Fig. 1). The inoculation and treatment with SA induces an observable phenotype, namely a hypersensitive response. The treatment with either of these stimuli independently does not induce the hypersensitive response. Seehaus et al. identify a number of genes that have increased expression in cells in response to stimuli that induce the hypersensitive response as compared to those treatments that do not induce the hypersensitive response (see Figure 1, Figure 2, and p. 1227).

Seehaus et al. do not teach a method wherein the plant cells comprise Ajuga reptans cells. Seehaus et al. do teach that their methodology is generally useful for the study of plant pathogen interactions, and has particular advantages in that many samples can be analyzed simultaneously (p. 1230, second column).

Tanaka et al. teach methods of gene search and isolation of genes associated with hairy root induction in an effort to better understand hairy root disease in Ajuga reptans (p. 95 and throughout).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methodology taught by Seehaus et al. for the further study of hairy root induction and hairy root disease. One would have been particularly motivated to study this disease of dicotyledonous plants in order to better understand the disease, and to use the methods taught by Seehaus et al. because Seehaus et al. particularly suggest the extension of

this methodology for the study of additional plant pathogens, and they expressly teach that their methodology has particular advantages such as the simultaneous comparison of a number of samples. Thus, in light of the teachings of the Seehaus et al. in view of Tanaka et al., the instant invention is prima facie obvious.

12. Claims 3 and 10 rejected under 35 U.S.C. 103(a) as being unpatentable over Seehaus *et al.* in view of van der Heijden *et al.* (Plant Cell Reports (1988) 7:51-54).

Seehaus et al. teach a method of identifying a gene associated with a desired phenotype, said method comprising the steps of:

(a) providing a plurality of cell cultures, each comprising plant cells capable of exhibiting said desired phenotype (p. 1226, "Biological material");

(b) contacting the cells of step (a) with a stimulus that (i) induces said cells to exhibit said phenotype or (ii) does not induce said cells to exhibit said phenotype (p. 1226);

(c) determining the presence of the desired phenotype in cells of step (b); and

(d) identifying a gene in said cells that has increased expression in response to stimuli that induce said phenotype but does not have increased expression in response to stimuli that do not induce said phenotype, wherein said identified gene is associated with said desired phenotype.

Seehaus et al. teach a method for analyzing the differential expression of genes in plant cell cultures, in particular soybean cell cultures. They provide a plurality of cell cultures, including control cultures, cultures that have been treated with salicylic acid, cultures that have been inoculated with Pseudomonas syringae pv. glycinea expressing the avrA gene, and cultures that were both inoculated and treated with SA (Fig. 1). The inoculation and treatment with SA

induces an observable phenotype, namely a hypersensitive response. The treatment with either of these stimuli independently does not induce the hypersensitive response. Seehaus et al. identify a number of genes that have increased expression in cells in response to stimuli that induce the hypersensitive response as compared to those treatments that do not induce the hypersensitive response (see Figure 1, Figure 2, and p. 1227).

Seehaus et al. do not teach a method wherein the phenotype is the production of terpenes or wherein the stimulus comprises a preparation from *Candida albicans*. Seehaus et al. do teach that their methodology has particular advantage that many samples can be analyzed simultaneously (p. 1230, second column), and teach that differential display is a "powerful tool" to identify new induced gene in plant-pathogen interactions (abstract).

Van der Heijden et al. teach that treatment of plant cells with *Candida albicans* elicitor preparation causes a rapid accumulation of antimicrobial active triterpenes (Abstract; p. 54, second column and table 4).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have utilized the methodology taught by Seehaus et al. study the effects of *Candida albicans* elicitor preparation on gene expression in plant cells. Such a method would have resulted in the detection of genes associated with the phenotype of terpene production, and particularly in the isolation of genes that are associated with terpene production. One would have been motivated to combine the methods of Seehaus et al. and van der Heijden et al. in order to have further elucidated the biochemical and molecular response of plant cells to *Candida albicans* and to further understand terpene synthesis in plants, especially in light of the demonstration by van der Heijden *et al.* that the terpenes produced have antimicrobial activity.

One would have been motivated to use the methods taught by Seehaus et al. because Seehaus et al. particularly expressly teach that their methodology has particular advantages such as the simultaneous comparison of a number of samples and treatments at one time, and Seehaus *et al.* describe their method as a powerful tool for the identification of new induced genes. Thus, in light of the teachings of the Seehaus et al. in view of Van der Heijden et al., the instant invention is prima facie obvious.

Conclusion

13. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (703) 306-5824. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 and (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Juliet C Switzer
Examiner
Art Unit 1634

October 17, 2003